#RxSummit

Impact of Abuse-Deterrent Formulations of Opioids

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Learning Objectives

- Understand the history of abuse-deterrent opioid development
- Understand the importance and challenges of developing and testing successful abuse-deterrent opioids
- Understand the importance and challenges of assessing the impact of abuse-deterrent opioids

Agenda

- FDA work to support the development of abuse-deterrent formulations of opioids
  - Abuse-Deterrent Opioids Draft Guidance
  - Regulatory decisions
- Progress in use of abuse-deterrent formulations of opioids
- Challenges in the development of abuse-deterrent formulations of opioids

Overall Messages

- Important work has been done to encourage the development and use of successful abuse-deterrent formulations of opioids
  - FDA is applying principles in draft Guidance to regulatory decisions
  - Draft Guidance is stimulating new development
  - Meaningful progress requires systematic, scientifically rigorous and flexible approach
  - Challenges remain before any one abuse-deterrent technology can be adopted

Overall Messages (cont)

- Work on ADF development is one part of the FDA efforts to confront prescription drug abuse
  - **Improving drugs used to treat pain**
    - Abuse-deterrent formulations of opioids
    - New classes of pain drugs that lack abuse risk
  - **Improving safe use of opioids**
    - Improved education of prescribers and patients to reduce risk of abuse
    - Improved surveillance to understand use of opioids
    - Improved use of packaging and storage of opioids
  - **Improving treatment of opioid abuse**
  - **Improving treatment of opioid overdose**
    - Naloxone autoinjector approval

Draft Guidance on Abuse-Deterrent (AD) Formulation Development of Opioids

**"GUIDANCE FOR INDUSTRY
ABUSE DETERRENT OPIOIDS—EVALUATION AND LABELING", JANUARY 2013**

Draft Guidance on Abuse-Deterrent (AD) Formulations of Opioids

- Early experience with AD formulation development
  - Focus of development on crush-resistant/extraction-resistant technologies and addition of aversive products (e.g., soaps, naloxone)
  - No broad claims for abuse-deterrence in and drug labels
  - Some studies included in labels (e.g., Oxecta)
  - No robust evaluation of impact of the formulation in real world setting

Draft Guidance on AD Opioid Formulations (cont)

- Follows earlier related draft Guidance: "Assessment of Abuse Potential of Drugs", issued January 2010
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf
- Discusses use of safety information from all areas of drug development, including brief discussion of abuse-deterrent formulations

Draft Guidance on AD Opioid Formulations (cont)

- Initial focus is on opioids
- Part of work to create safer opioids
- Guidance on AD formulation development was promised as part of ONDCP Rx Drug Abuse Plan (2011)
- Guidance on ADF development mandated under FDASIA*
  - Goal date January 9, 2013

* Food and Drug Administration Safety and Innovation Act

Draft Guidance on AD Opioid Formulations: Released January, 2013

- **Purpose**: Reflect the state of the science of abuse deterrence (relatively new), and the need for flexible approach while still applying a rigorous, science-based standard in evaluation and labeling of drugs as data accumulates

Draft Guidance on AD Opioid Formulations : Highlights

- **Goals**: Two over-arching goals:
  - Provide incentive for developing successful abuse-deterrent formulations of opioids
  - Assure appropriate development and availability of generic drugs, reflecting their importance in US healthcare
- **Accomplishing Goal**:
  - Use labeling to identify drugs with successful AD formulations to encourage their use

Highlights of Draft Guidance on AD Opioid Formulations

- Lays out development roadmap:
  - Scientific studies relevant to assessing impact of formulation on abuse
  - Assessments FDA will use when looking at study data
- Lays out impact of AD data on opioid labeling, including claim for abuse-deterrence
  - Goal to incentivize meaningful AD formulation development
- Identifies areas of additional scientific needs

Label Claims for Opioids with AD Formulations

- Grouped according to source and type of data
  - Tier 1: Physical/Chemical Barriers to Abuse
    - Examples: data on crushing and extraction
  - Tier 2: PK Data
    - Clinical serum concentrations (e.g., Tmax, Cmax)
  - Tier 3: Demonstration of Reduced Abuse Potential
    - Clinical Abuse Potential Studies
  - Tier 4: Demonstration of Reduced Abuse
    - Postmarketing data on use and misuse of marketed product
- Differs according to technology used to create formulation

Additional Scientific Work Needed

- Understanding the quantitative link between blood levels of drug from AD formulations and risk of abuse in the community
- Understanding the best ways to analyze clinical data on abuse
- Understanding the best ways to predict the impact of formulations on rates of abuse in the community
    - Important for generic drug development

Unresolved Issues

- Does not address how FDA will approach generic drug evaluation, approval, and withdrawal
- Does not set 'bright line' standard of what constitutes meaningful 'abuse deterrence'
  - Will need more experience before we can set such a standard
  - Need more data on the link between non-clinical and pre-market studies and post-market impact on abuse, overdose, and death

Since Release of Draft Guidance

- Considerable industry interest in developing AD formulations of opioids
  - Multiple meetings with FDA and manufacturers
- Importantly, new approaches to AD opioid development are being proposed/tested, in addition to crush-resistant/extraction-resistant technologies

Regulatory Actions

1. OXYCONTIN AND OPANA ER
2. EXTENDED-RELEASE AND LONG-ACTING OPIOIDS RELABELING AND POST-MARKETING REQUIREMENT
3. ZOHYDRO

Actions on Oxycontin & Opana ER

- April 16, 2013: Oxycontin granted labeling as abuse-deterrent
  - The new label indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)
- May 10, 2013: Opana ER determined not to have demonstrated abuse-deterrent properties
- Decisions based on scientific data from each application separately, drawing on principles from draft Guidance

Action on Zohydro

- **Zohydro**
  - Member of Extended-Release/ Long-Acting (ER-LA) Class of opioids
  - Similar doses, anticipated risks of abuse and anticipated uses as other ER-LA opioids
  - Meets statutory requirements for approval
- **Identifiable benefits for patients and prescribers**
  - Provides additional choice for patients and prescribers
  - Allows patients who need high doses of hydrocodone to avoid use of acetaminophen and liver toxicity and take fewer pills
- **Label reflects newly revised ER-LA opioid labeling**
  - Responsive to Advisory Committee concerns about ER-LA opioids
  - Increased safety information
  - New, focused indication to better guide decisions about who could benefit
  - Required additional safety studies

Action on Zohydro: Why Didn't FDA Require AD Formulation?

- Abuse-deterrent technologies are not a silver bullet and are still early stages of development
  - One approved product that is abuse deterrent (Oxycontin)
    - Important first step, but abuse of Oxycontin still occurs
    - Not effective at reducing primary route of abuse (oral)
    - Can be defeated using easily available means
  - At least one other opioids (Opana ER) that incorporate similar technologies designed to deter abuse failed to demonstrate an impact on abuse
    - This is not straightforward!
  - Premature to require early technology when what is needed is improved science and technology

Ongoing Challenges

Focus on AD Formulations

- Continued scientific progress on AD formulations
  - FDA laboratory working on AD formulation science
  - FDA support of external scientific work on AD formulations
- Continued work to assess impact of AD formulations on actual abuse and misuse of opioids
  - FDA epidemiologists working on improving tools FDA uses to assess impact of AD formulation of Oxycontin in US market
  - FDA and USG working to improve the surveillance databases used to assess impact of AD formulations in US market
- Refinement of our guidance on the development of ADFs:
  - Pathway to the development of ADFs of generic drugs
  - Refinement of what is needed to demonstrate meaningful abuse-deterrence

Focus on Other Efforts to Address Opioids Abuse

- Abuse-deterrent formulations are one part of many actions that are needed to address opioid abuse

- **Improving drugs used to treat pain**
  - Abuse-deterrent formulations of opioids
  - New classes of pain drugs that lack abuse risk
- **Improving safe use of opioids**
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Conclusions

- Important work has been done to encourage the development and use of successful abuse-deterrent formulations of opioids
- Work to encourage abuse-deterrent formulations of opioids is one of many activities FDA is doing to improve the safe use of opioid drugs
- FDA will continue to act with the available data to seek a balance between the needs of pain patients and the need to reduce prescription drug abuse